POSTER NUMBER 451

Efficacy and Safety of Methylnaltrexone for Opioid-Induced Constipation in Patients With Chronic Noncancer Pain: A Placebo Crossover Analysis

Eugene R. Viscusi, MD[1]; Andrew C. Barrett, PhD[2]; Craig Paterson, MD[2]; William P. Forbes, PharmD[2]
[1]Thomas Jefferson University, Philadelphia, PA, USA; [2]Salix Pharmaceuticals, Inc., Raleigh, NC, USA

INTRODUCTION

- Opioid-induced constipation (OIC) is a prevalent adverse effect of chronic opioid therapy and has been reported in 41% to 81% of patients with chronic noncancer pain taking long-term opioids[1,2]
  - OIC can be more distressing to patients receiving opioids than the underlying pain syndrome[3]
  - Unlike other adverse effects of opioid use (eg, nausea and vomiting), which usually resolve after continued therapy, patients develop little or no tolerance to OIC[4]
- Treatment of OIC with laxatives is inadequate in a substantial portion of patients, as these agents do not target the underlying pathophysiology of OIC,[5] which involves opioid activation of μ-opioid receptors in the gastrointestinal tract[6]
- Methylnaltrexone (MNTX; Relistor®, Salix Pharmaceuticals, Inc., Raleigh, NC, USA) is a selective, peripherally acting μ-opioid receptor antagonist that has restricted ability to cross the blood-brain barrier[7,8]
  - MNTX efficacy and safety in patients with chronic, nonmalignant pain and OIC has been demonstrated in a randomized, placebo-controlled, phase 3, 4-week study (RCT) with efficacy and tolerability maintained for up to an additional 8 weeks in an open-label extension (OLE) study[9,10]

OBJECTIVE

To examine the reproducibility of findings from the RCT, data from placebo-treated patients who crossed over to MNTX treatment in the OLE were analyzed

METHODS

Study Design

- Patients treated with placebo in the RCT and crossed over to receive MNTX in an OLE
  - In the RCT, patients received subcutaneous MNTX 12 mg once daily (QD), MNTX 12 mg once every other day (QOD), or placebo for 4 weeks[9] and, in the OLE, patients received subcutaneous MNTX 12 mg as needed (PRN; maximum, QD) for 8 weeks[10]

Study Population

- Patients eligible for RCT were ≥18 years of age with chronic pain (lasting ≥2 months prior to enrollment and taking opioids ≥1 months [average daily dose ≥50 mg oral morphine equivalents for ≥2 weeks]), caused by a noncancer condition, and OIC (<3 rescue-free bowel movements [RFBMs] per week with ≥1 of the following signs and symptoms: hard or lumpy stools, straining, or a sensation of incomplete evacuation)
  - Patients discontinued all laxatives taken prior to enrollment; rescue laxatives (bisacodyl tablets taken ≥4 hours after study drug administration and only 1 dose allowed within 24-hour period) were permitted if the patients had no bowel movements for 3 consecutive days during RCT or OLE

Assessments

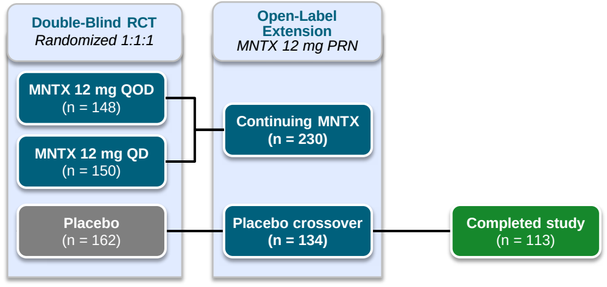
- Efficacy outcomes evaluated during both phases using patient-reported diary information, which included number and time of bowel movements and rescue laxative use
  - Coprimary efficacy endpoints in RCT: percentage of patients with RFBMs within 4 hours of the first dose and percentage of injections resulting in any RFBM within 4 hours of dose administration
  - Secondary efficacy endpoint: percentage of patients experiencing ≥3 RFBMs/week and 1 RFBM increase over baseline
- Safety assessments included monitoring of adverse events (AEs), clinical laboratory tests, vital signs, and concomitant medications

RESULTS

Patient Disposition and Demographics

- 460 patients received MNTX 12 mg QD (n = 150), MNTX 12 mg QOD (n = 148), or placebo (n = 162) in the 4-week RCT
  - Of the 162 patients who had received placebo in the RCT, 134 patients crossed over to open-label MNTX treatment during the extension phase (Figure 1)

Figure 1. Patient Disposition



- The 134 patients in the crossover group were predominantly white (88.8%) and female (64.2%), with a mean (SD) age of 50.3 (10.8) years and back pain as the primary pain condition (Table 1)

Table 1. Baseline Characteristics

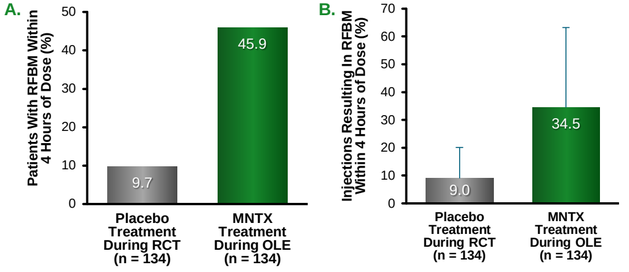
Characteristic		Placebo Crossover Patients (n = 134)
Primary pain condition, n (%)	Back pain	78 (58.2)
	Other	56 (41.8)
Baseline morphine equivalent dose, mg/day	Mean (SD)	214.6 (199.3)
	Median	150.0
Duration of OIC, mo, mean (SD)		340.4 (305.0)
Baseline average bowel movements per week, mean (SD)		1.1 (0.8)

Efficacy Outcomes

- 13 of 134 patients (9.7%) experienced a RFBM within 4 hours of first placebo dose during the RCT versus 61 (45.9%) who experienced a RFBM within 4 hours of first MNTX dose in the OLE (Figure 2)
  - Similarly, on average, more injections with MNTX in the OLE resulted in RFBM within 4 hours of dose versus injections with placebo in the RCT (34.5% and 9.0%, respectively)

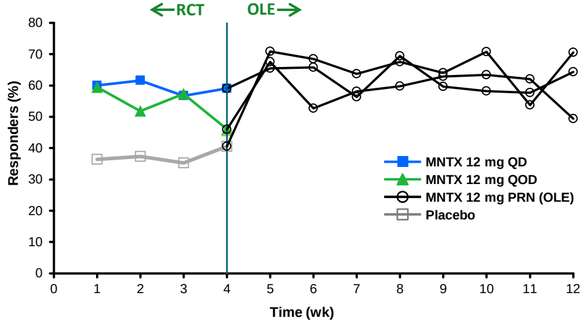
RESULTS

Figure 2. (A) RFBM Within 4 Hours of Administration of the First Dose of RCT Placebo or OLE MNTX; (B) Percentage of Injections That Resulted in Any RFBM Within 4 Hours of Administration of the Dose of RCT Placebo or OLE MNTX



- When expressed according to percentage of patients experiencing ≥3 RFBMs per week and ≥1 RFBM increase over baseline, weekly values ranged from 35% to 41% during placebo treatment in the RCT, suggesting a lack of tolerance development to OIC over time (Figure 3)
  - However, with MNTX treatment, this percentage increased to >70% within the first week (Week 5) and remained relatively stable throughout the study

Figure 3 . Percentage of Patients With Weekly Number of RFBMs ≥3 and an Increase of ≥1 RFBM From Baseline



Solid symbols during the RCT phase indicate statistically significant difference versus placebo ($P < 0.05$).

RESULTS

Safety

- Overall incidence of AEs were reported in 32.8% of patients during placebo treatment in the RCT versus 43.3% of patients during 8 weeks of MNTX treatment in the OLE (Table 2)
  - Abdominal pain, nausea, and urinary tract infections were the most common AEs during the OLE

Table 2. Summary of Adverse Events

Adverse Events, n (%)		Placebo Treatment During RCT (n = 134)	MNTX Treatment During OLE (n = 134)
Any AEs		44 (32.8)	58 (43.3)
Most common AEs[a]	Abdominal pain	2 (1.5)	13 (9.7)
	Nausea	9 (6.7)	7 (5.2)
	Urinary tract infection	2 (1.5)	7 (5.2)
	Diarrhea	4 (3.0)	6 (4.5)
	Hyperhidrosis	1 (0.7)	6 (4.5)
	Hypertension	0	5 (3.7)
	Back pain	1 (0.7)	4 (3.0)
	Influenza	0	4 (3.0)
	Rhinorrhea	1 (0.7)	4 (3.0)
	Sinusitis	0	4 (3.0)
	Upper abdominal pain	5 (3.7)	4 (3.0)

[a]Reported in ≥5% of patients.

- Serious AEs were reported in 1 patient during placebo treatment (musculoskeletal chest pain) and 4 patients during MNTX treatment (pneumonia in 2 patients; gastroenteritis and hypertension in 1 patient; and mental status change in 1 patient); none were considered drug-related

CONCLUSIONS

- **This placebo-crossover study establishes the reproducibility and durability of MNTX for treatment of OIC in chronic noncancer pain**
- **Findings during placebo treatment in the RCT further establish the nature of OIC and support that little or no gastrointestinal tolerance develops over time**

REFERENCES **1.** Kalso E, et al. *Pain*. 2004;112:372-380. **2.** Bell TJ, et al. *Pain Med*. 2009;10(1):35-42. **3.** Cook SF, et al. *Aliment Pharmacol Ther*. 2008;27(12):1224-1232. **4.** Clemens KE, et al. *Ther Clin Risk Manag*. 2010;6:77-92. **5.** Pappagallo M. *Am J Surg*. 2001;182(5A Suppl):11S-18S. **6.** DeHaven-Hudkins DL, et al. *Pharmacol Ther*. 2008; 117(1):162-187. **7.** Rosow CE, et al. *Clin Pharmacol Ther*. 2007;82(1):48-53. **8.** Russell J, et al. *Eur J Pharmacol*. 1982;78(3):255-261. **9.** Michna E, et al. *J Pain*. 2011;12(5):554-562. **10.** Blonsky E, et al [abstract no. 149]. *Reg Anesthes Pain Med*. 2009;34(5):98.

Disclosures: ERV received honoraria and consulting fees from Salix Pharmaceuticals, Inc. ACB and CP are employees of and hold stock in Salix Pharmaceuticals, Inc. WPF is an officer and employee of and holds stock in Salix Pharmaceuticals, Inc.

Acknowledgment: Technical editorial and medical writing assistance was provided under the direction of the authors by Pratibha Hebbar, PhD, Synchrony Medical Communications, LLC, West Chester, PA. Funding for this support was provided by Salix Pharmaceuticals, Inc., Raleigh, NC.

Research funded by:
Salix® Pharmaceuticals, Inc.